REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 398, 402, 403, 410, 414-416 and 424-447 are pending in the application. Claims 403, 415, 426, 428, 435, 436 and 443-447 are withdrawn from consideration as being directed to non-elected subject matter.

Claims 398, 402, 410 and 414 are amended, claims 380-397, 399-401, 404-409, 411-413 and 417-423 are canceled, and new claims 424-447 are added by the present amendment. Of the newly added claims, claims 426, 428, 435, 436 and 443-447 are identified as "Withdrawn - New" in accordance with MPEP §714 II C (E).

Support for the claim amendments and new claims can be found in the specification at, *e.g.*, the following locations of the published international application from which this case entered the US national stage (WO 2005/058941):

Claim 398 - paragraphs 0009, 0013 and 0023, and Table 12 (p. 63);

Claims 424-426 - paragraph 0095;

Claim 427 - paragraphs 0023 and 0110;

Claims 428 and 447 - paragraph 0024;

Claims 429, 430, 434 and 436 - paragraph 0117;

Claims 431, 438 and 444 - Table 13 (p. 63);

Claims 432, 433, 435, 439-441 and 445 - Table 2 (p. 48);

Claim 437 - paragraphs 0042-0044, Table 12 (p. 63), and Examples 1, 2 and 6;

Claims 442 and 446, brief description of sequences at pp. 12 and 15, respectively; and

Claim 443 - paragraphs 0042-0044, Table 12 (p. 63), and Examples 10 and 11.

Claims 402, 410 and 414 are amended only to modify the claim dependency and for consistency with the amendments made to claims from which they depend. No new matter is added by the present amendment.

Election/Restriction and Status of Claims

The present Office Action indicates that claims 403 and 415, among others, have been withdrawn from further consideration as being drawn to nonelected species. Applicants submit that claims 403 and 415 should not be withdrawn. In the response filed March 5, 2009,

Applicants elected a peptide immunogen having the amino acid sequence of SEQ ID NO:2 (*i.e.*, DAEFRHD-C). This is an Aβ1-7 fragment with a C-terminal cysteine residue. Claims 403 and 415 recite "wherein the Aβ fragment is residues 1-7 of Aβ". Accordingly, Applicants submit that claims 403 and 415 read on the elected species. Further, Applicants note that neither claim 402 nor 414, which recite selection of the Aβ fragment from a group of specific residues, including residues 1-7, were not withdrawn in the present Office Action. Thus, Applicants respectfully request that claims 403 and 415 be considered in connection with the present response.

Claim Rejections - 35 USC §112, 2nd Paragraph

Claims 398-402, 404-408, 410-414 and 416 are rejected under 35 USC 112, second paragraph as allegedly being indefinite because claims 398 and 404 recite "analogs of Aβ peptide."

Without agreeing with the Examiner, Applicants have amended claim 398 to delete reference to "analogs of Aβ peptide." Claim 404 has been canceled. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Claim Rejections - 35 USC §112 - 1st Paragraph

Claims 398-402, 404-408, 410-414 and 416 are rejected under 35 USC 112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Examiner states that claims 398 and 404 recite "analogs of Aβ peptide," and that the specification provides no limiting definition for the term "analog" or otherwise discloses any analogs in a way as to reasonably convey to one of skill in the art that Applicants were in possession of such subject matter at the time the application was filed.

Without agreeing with the Examiner, Applicants reiterate that claim 398 has been amended to delete reference to "analogs of Aβ peptide," and that claim 404 has been canceled. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Claim Rejections - 35 USC §103

Claims 398-402, 404-408, 410-414 and 416 are rejected under 35 USC 103(a) as allegedly being unpatentable over **Brinkley**, *Bioconjugate Chemistry*, 3:2-13 (1992) in view of

Shimizu *et al.*, *Journal of Neuroscience Research*, 70:451-461 (2002), in view of **Askelof** *et al.*, *Proc. Natl. Acad. Sci. USA*, 87:1347-1351 (1990), and further in view of US Patent No. 4,882,317 to **Marburg** *et al.* In particular, the Examiner states that Brinkley discloses a protein conjugated to a second molecule, which is usually a thiol-containing protein, and the reaction of the protein with glutathione, mercaptoethanol, or other low-molecular weight thiol to consume excess modification reagent. The reaction with a low-molecular weight thiol (discussed at page 10, column 2, paragraph 3, of Brinkley) allegedly reads on the capping features of the instant invention. The Examiner further states that Shimizu discloses a conjugate comprising an Aβ fragment, that Askelof discloses a conjugate comprising a CRM_{197} carrier protein, and that Marburg discloses the use of N-acetylcysteamine as a capping reagent.

Applicants respectfully traverse. The use of capping reagents may disrupt the ability of the resulting conjugate to function as an immunogenic agent having the desired properties of the "carrier effect." *See* paragraph 0008 of the specification. Thus, one of skill in the art could not have predicted the effect of a capping reaction on the ability of a CRM_{197} carrier protein to induce an immune response against a conjugated immunogen, *ab initio*, and nothing in the cited art teaches or suggests that retention of such function was the predicted result.

The Presently Claimed Invention

The presently claimed invention is directed to an immunogenic conjugate comprising an Aβ fragment peptide immunogen covalently attached to a CRM_{197} carrier protein, and further comprising a capping molecule covalently attached to a derivatized functional group of the carrier protein, whereby the functionality of the carrier protein is preserved such that it retains its ability to elicit the desired immune responses against the peptide immunogen that would otherwise not occur without a carrier.

Brinkley (Bioconjugate Chemistry)

Brinkley discusses methods for preparing protein conjugates with dyes, haptens, and cross-linking reagents. *See* p. 2, 1st column, 2nd paragraph. Brinkley includes a section discussing experimental methods for conjugating amine-reactive and thiol-reactive probes to proteins. *See* p. 10, 1st column, 1st paragraph. The probes, which include haptens (p. 10, 1st

column, 2nd paragraph), are referred to in the experimental methods as protein-modification reagents. *See* "Step 2" at p. 10, 1st column, 4th paragraph, and 2nd column, 3rd full paragraph. Brinkley reports that upon completion of the conjugation reaction between the protein-modification reagent and the protein, an excess of a low molecular weight thiol (*e.g.*, glutathione or mercaptoethanol) can be added to the reaction mixture to consume excess modification reagent (p. 10, 2nd column, 3rd full paragraph), which is then separated from the conjugate in "Step 3" (p. 10, 2nd column, 6th full paragraph). Thus, Brinkley discusses consuming excess hapten in the reaction mixture, but does not discuss capping reactive functional groups of the carrier protein.

Shimizu et al. (J. Neuroscience Research)

Shimizu discusses the conjugation of an isomerized A-beta peptide to maleimide-activated KLH. *See* page 452, 2nd column, last paragraph. Shimizu makes no reference to capping unreacted functional groups of the carrier protein in an immunogenic conjugate.

Askelof et al. (PNAS)

Askelof discusses the conjugation of a peptide (a pertussis toxin subunit) to CRM_{197}. *See* abstract. Askelof makes no reference to capping unreacted functional groups of the carrier protein in an immunogenic conjugate.

Marburg et al. (US Patent No. 4,882,317)

Marburg discusses the conjugation of pneumoccal polysaccharides to carrier proteins. *See* abstract. Marburg indicates that the proteins of the invention are those of proven safety and demonstrable immunogenicity, but are not limited to any particular type. *See* Col. 6, lines 3-5. However, Marburg exemplifies the use of only a single carrier protein, *N. Meningitidis* B Serotype Outer Membrane Protein (NMP) (*see, e.g.*, Example 3), in the preparation of capped pneumoccal polysaccharide conjugates.

The Use of Capping Molecules and Preservation of the "Carrier Effect"

A distinguishing feature of the presently claimed invention is the inclusion of a capping molecule covalently attached to the derivatized functional group of the CRM_{197} carrier

protein, *and* the concurrent preservation of the functionality of the carrier protein to induce an immune response against the conjugated peptide immunogen via the "carrier effect."

As discussed in the specification, a disadvantage of the conventional techniques for the generation of immunogenic conjugates is that the introduction of reactive sites into amino acid side chains of the carrier protein produces reactive sites that, if not neutralized, are free to undergo unwanted reactions *in vitro* (thereby adversely effecting the functionality or stability of the conjugate) or *in vivo* (thereby posing a potential risk of adverse events in persons immunized with the conjugates). *See* paragraph 0008 of the published international application. Although capping can be accomplished using various known chemical reactions, the use of capping reagents may disrupt the ability of the resulting conjugate to function as an immunogenic agent having the desired properties of the "carrier effect." *Id.* Thus, the presently claimed invention is addressed to the problem of providing an immunogenic conjugate that has been capped to improve safety and stability, while also retaining the carrier protein's ability to elicit the desired immune response against the conjugated peptide immunogen that would otherwise not occur without a carrier protein.

The presently claimed invention is based, in part, on Applicant's discovery that a capping molecule can be used with the claimed CRM_{197} carrier protein to avoid unwanted side reactions that may detrimentally impact the stability or safety of an immunogenic conjugate, while also preserving the conjugate's ability to elicit a desired immune response against the attached peptide immunogen. Immunogenic conjugates comprising a peptide immunogen coupled to a CRM_{197} carrier protein, and capped as recited in the presently claimed invention are exemplified in the specification at Examples 1, 2 and 10. The immunogenicity of a number of these capped conjugates is demonstrated in Examples 6 and 7, confirming that the functionality of the carrier protein is preserved and the desired immune response is elicited.

The Cited Art does Not Teach Capping & Preservation of the "Carrier Effect" in CRM_{197}

Brinkley, the primary reference, provides no guidance to the skilled artisan on capping unreacted functional groups of the carrier protein. Rather, Brinkley discusses consuming excess modification reagent (*e.g.*, immunogen) in the reaction mixture. The excess modification reagent that is reacted with glutathione or mercaptoethanol is not part of the

immunogenic conjugate, as demonstrated by its separation from the conjugate in "Step 3". Thus, Brinkley neither teaches nor suggests capping reactive functional groups of the carrier protein, nor preservation of the functionality of the carrier to elicit an immune response via the "carrier effect," as presently claimed.

Neither Shimizu nor Askelof address this deficiency of Brinkley because neither reference discusses capping in any capacity.

Similarly, Marburg provides no guidance to the skilled artisan because Marburg neither discusses nor exemplifies the use of CRM_{197} as a carrier protein. Marburg exemplifies the use of only a single carrier protein, NMP, in the preparation of a capped immunogenic conjugate. As mentioned above, the use of chemical capping reagents to inactivate the unreacted derivatized functional groups on the carrier protein may be disruptive to the functionality of the resulting immunogenic conjugate. Thus, the single exemplary carrier of Marburg would not have provided the skilled artisan with a reasonable expectation that the CRM_{197} carrier protein recited in independent claims 398, 437 and 442 could be capped while preserving the functionality of the carrier such that it retains its ability to elicit the desired immune response against the peptide immunogen that would otherwise not occur without a carrier, as claimed.

In view of the foregoing, Applicants submit that the presently claimed invention is patentable over the cited art. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Nonstatutory Obviousness-Type Double Patenting Rejections

Claims 398-402, 404-408, 410-414 and 416 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 384-396 of copending Application No. 10/583,464 in view of Shimizu, *supra*.

Without agreeing with the Examiner, Applicants will consider submitting a terminal disclaimer, if appropriate, to obviate this rejection upon an indication that the presently claimed invention is otherwise allowable.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-838-2000.

Respectfully submitted,

Lance A. Termes
Reg. No. 43,184

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel: Silicon Valley Office (650) 838-2000
Fax: Charlotte Office (704) 444-1111
LAT:mrc

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